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ScienceDirect
European Journal of Obstetrics & Gynecology and Reproductive Biology 139 (2008) 169–175
ejog European Journal of Obstetrics & Gynecology and Reproductive Biology
www.elsevier.com/locate/ejogrb

The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia—A long-term follow-up study

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Received 1 October 2007; received in revised form 14 December 2007; accepted 23 February 2008

Abstract

Objectives: Medical treatment of non-atypical endometrial hyperplasia with oral progestogens has limited efficacy and poor compliance. A levonorgestrel-releasing intrauterine system (LNG-IUS) has been shown to successfully treat hyperplasia in small-sized studies. Our aim was to examine the effectiveness of LNG-IUS in a larger study with long-term follow up.
Study design: Prospective observational study of 105 women diagnosed with endometrial hyperplasia and treated with LNG-IUS between 1999 and 2004 at a University Teaching hospital. Baseline characteristics and outpatient endometrial Pipelle sampling were undertaken at 3 and 6 months post LNG-IUS insertion and 6-monthly intervals thereafter in all cases. Outcome included histological data derived from both Pipelle and uterine histologies at 1 and 2 years LNG-IUS therapy.
Results: LNG-IUS achieved endometrial regression in 90% (94/105) of cases by 2 years, with a significant proportion (96%, 90/94) achieving this within 1 year. Regression occurred in 88/96 (92%) of non-atypical and 6/9 (67%) of atypical hyperplasias, and in all 22 cases of endometrial hyperplasia associated with HRT. Regression rates did not differ between histological types of hyperplasia. Twenty-three women (22%) underwent hysterectomy of which 13 were indicated and 10 were performed at patient request despite regressed endometrium. Two cases of cancer (one uterine and one ovarian) were identified.
Conclusion: LNG-IUS is highly effective in treating endometrial hyperplasia. Beneficial effects are observed by the majority within 1 year. Treatment can be reliably monitored through regular 6-montly outpatient endometrial Pipelle surveillance. LNG-IUS treatment of non-atypical hyperplasias is likely to reduce the number of hysterectomies performed in this subgroup.

Keywords: Endometrial hyperplasia; Levonorgestrel; Intrauterine devices; Medicated; Therapy; Mirena

1. Introduction

Endometrial hyperplasia may be divided into three principal histological categories listed in the order of ascending architectural and cytological abnormality: simple, complex and atypical hyperplasia [1]. Cytological atypia is the most important prognostic factor for progression to carcinoma [2]. Around 1–3% of non-atypical hyperplasias progress to endometrial carcinoma, over a mean duration of 10 years. In contrast, 8–30% of atypical hyperplasias progress to carcinoma over a mean duration of 4 years [3]. Pooling three observational studies [4–6] the rates of spontaneous regression after expectant treatment for non-atypical ($n = 129$) and atypical hyperplasia ($n = 28$) are around 72% and 54%, respectively.

The objectives of treating women with endometrial hyperplasia are to reduce abnormal bleeding symptoms and to prevent progression to endometrial cancer [6–8]. In view of an increased oncogenic potential with atypical endometrial hyperplasia, hysterectomy is generally recommended unless

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0301-2115/$ – see front matter
doi:10.1016/j.ejogrb.2008.02.022

fertility issues or significant risk factors for surgery preclude this. However, for non-atypical endometrial hyperplasia, there is debate as to whether hysterectomy is 'over-treatment' given the low risk of malignant transformation, high probability of possible spontaneous resolution, low risk of coexistent uterine cancer and high therapeutic responsiveness to oral progestogen therapy. Nonetheless, oral progestogens are associated with poor compliance and systemic side effects that may limit overall efficacy [6–8].

Levonorgestrel-releasing intrauterine system (LNG-IUS) may be used to successfully treat endometrial hyperplasia without incurring the disadvantages of oral progestogens. This finding has been demonstrated in two recently published observational studies [9,10], together with a systematic review [11] that included four limited sized studies [12–15]. Our objective was to examine the effectiveness of LNG-IUS to treat endometrial hyperplasia in a larger prospective observational study with a long-term follow-up period.

2. Methods

All women participating in this study had presented to our hospital (Birmingham Women's Hospital, England) for the investigation of abnormal uterine bleeding. Their reasons for referral included: women aged 40 years and over with heavy menstrual bleeding or intermenstrual bleeding unresponsive to medical therapies (such as tranexamic acid, combined oral contraceptive or oral progestins), post-menopausal bleeding and unscheduled bleeding whilst on hormone replacement therapy or tamoxifen. Natural menopause was recognised to have occurred if there had been at least 12 consecutive months of amenorrhoea, for which there was no other obvious pathological or physiological cause. Clinical investigation involved transvaginal pelvic sonography, outpatient endometrial Pipelle sampling (Laboratoire C.C.D, Paris, France) and outpatient hysteroscopy in all cases. Intrauterine polyps that were identified at hysteroscopy were removed using outpatient local anaesthetic Versapoint® (Gynecare, Ethicon Inc. USA) polyp resection or blind polypectomy techniques.

Endometrial hyperplasia was subdivided into three categories: simple, complex and atypical. For the purposes of this study, we grouped simple atypical and complex atypical hyperplasias as one atypical hyperplasia group. The criteria for diagnosing endometrial hyperplasia and endometrial regression of hyperplasia following LNG-IUS use was as we [16] and others [1,10,17,18] have previously described. Typically, LNG-IUS resulted in atrophy of glands separated by plump, polygonal, pseudodecidualised stromal cells. These were accompanied by varying degrees of secretory glandular changes and metaplasia of the lining epithelium. These changes have been collectively and loosely termed as ''regression'' of hyperplasia in this paper. This is not a defined histological entity except in the context of follow up of endometrial hyperplasia. Similar morphology can be seen with both oral progestogens and intrauterine progestogen (LNG-IUS) when used for other clinical indications.

Our study included cases where hyperplasia was only present in the endometrial polyp but not the background endometrium, a phenomenon also described by a previous study [19]. All histopathological diagnoses were undertaken by two experienced consultant histopathologists (TR, RG) working independently; referral to the other pathologist for a second opinion was made in cases where there was diagnostic doubt, and a mutual consensus was then achieved.

Throughout the study period (January 1999–January 2004) there were 114 women diagnosed with non-atypical hyperplasia. All were offered oral progestogens, LNG-IUS insertion (Mirena®, Schering Health Care, Burgess Hill, UK) or hysterectomy as part of our routine practice; those opting for LNG-IUS ($n = 105$) were included in our study cohort. Women diagnosed with atypical endometrial hyperplasia were recommended to undergo hysterectomy. Women who declined surgery or who were medically unfit to undergo surgery were offered oral progestogens or LNG-IUS insertion; the latter LNG-IUS treated group ($n = 9$) were included in our study cohort. Women diagnosed with non-atypical endometrial hyperplasia whilst using hormone replacement therapy (HRT) were offered either withdrawal of HRT and LNG-IUS, withdrawal of HRT and oral progestagens, or HRT (either estrogen replacement therapy or continuous combined preparations) and LNG-IUS; those opting for combinations involving LNG-IUS ($n = 22$) were included in our study cohort.

2.1. Baseline data and study design

Insertion of LNG-IUS took place between January 1999 and January 2004. For all women in the study ($n = 105$) anonymised baseline data were recorded on: histological subtype, sociodemographic characteristics (with emphasis on risk factors for endometrial hyperplasia such as parity, body mass index, diabetes, hypertension), use of exogenous hormones (e.g. hormone replacement therapy, tamoxifen), and presenting abnormal bleeding symptoms.

Study participants underwent regular outpatient clinic review and endometrial histological surveillance by outpatient Pipelle sampling. Histological surveillance was performed at 3-months and 6-months following LNG-IUS insertion, and continued thereafter at 6-monthly intervals in all cases ($n = 105$). For the purposes of this study, we present the outcome for participants at 1 and 2 years post LNG-IUS insertion, however, in clinical practice, we are continuing to prospectively record outcome beyond this time, even in cases that show endometrial regression.

LNG-IUS treatment was abandoned and hysterectomy recommended if:

(1) There was no histological evidence of partial or complete regression of the hyperplasia by 12 months of LNG-IUS use.
(2) There was histological evidence of endometrial cancer or progression of endometrial hyperplasia to atypia.
(3) There was reversion to the original endometrial histology showing hyperplasia following a period of endometrial regression.

The primary outcome was the proportion of women with complete regression of the endometrial hyperplasia according to both outpatient endometrial Pipelle and uterine histologies at hysterectomy. Secondary outcomes included time to disease regression, the proportion of women undergoing hysterectomy (histologically indicated or non-histologically indicated) and the accuracy of outpatient Pipelle compared to uterine histology at hysterectomy.

2.2. Statistical analysis

SPSS version 13 for Windows (Release 13.0, 1 Sep 2004, SPSS Inc.) was used. The significance of different histological subtypes and other covariates on time interval to regression was determined by Kaplan–Meier and Cox-regression survival analysis. A *P*-value less than 0.05 was considered statistically significant. Sensitivity, specificity and likelihood ratios were derived by constructing a 2 by 2 table and using standard techniques [20].

3. Results

3.1. Baseline characteristics

There were 105 women with endometrial hyperplasia (simple 16, complex 80, atypical 9) included in the 5-year study period. A summary of the baseline characteristics and presenting symptoms are shown in Table 1. The mean age was 54.5 ± S.D. 10.1 years (range 37–88). The study comprised 37 premenopausal and 68 postmenopausal women. Most women presented with postmenopausal bleeding ($n = 68$). Endometrial polyps were visualised in 36/105 (34%) cases at hysteroscopy. Hyperplasia in the endometrial polyp, but not in the background endometrium, occurred in 16% (17/105) of cases; all remaining cases had endometrial hyperplasia identified within the endometrium.

3.2. Endometrial regression at 2 years post LNG-IUS insertion

Fig. 1 summarises the outcome of the 105 hyperplasias that received LNG-IUS according to pre-treatment and 2-year *outpatient endometrial Pipelle histologies*. In contrast, Table 2 summarises the outcome of the study according to histological data derived from *both outpatient endometrial Pipelle and hysterectomy histologies* at 1 and 2 years post LNG-IUS insertion. The derivation of this data is explained in the footnotes to Fig. 1 and Table 2.

Outpatient endometrial Pipelle regression was observed in 94/105 cases, and of these, 87/94 continued to maintain endometrial regression at 2 years follow up (Fig. 1). Failed treatment, indicated by persisting Pipelle hyperplasia or hyperplasia that regressed then reverted to hyperplasia, occurred in 18/105 cases (Fig. 1).

Overall, 90% (94/105) of the study participants achieved endometrial regression according to combined outpatient Pipelle and hysterectomy histologies (Table 2). A significant proportion (96%, 90/94) had achieved this by 1 year of LNG-IUS use.

Table 1
Baseline characteristics ($n = 105$)

Characteristic	Size of parameter
Age (years)	Mean 54.5 (standard deviation 10.1, range 37–88)
Weight (kg)	Mean 86.0 (standard deviation 28.0, range 50–168
BMI kg/m^2	Mean 32.0 (standard deviation 8.8, range 18–67)
Characteristic	**Percentage of cases in study group (equals number of cases)**
Parity[a]	21% (22) Parity 0 43% (45) Parity 1 or 2 23% (24) Parity 3 or higher Mean 1.87; standard deviation 1.34, range 0–5
Menopausal status	35% (37) premenopausal; 65% (68) postmenopausal
Diabetes	18% (19)
Hypertension	30% (31)
Exogenous HRT	21% (22)
Exogenous tamoxifen	1% (1)
Abnormal bleeding symptoms on presentation	27% (28) Premenopausal, abnormal uterine bleeding 9% (9) Premenopausal, unscheduled bleeding with HRT 51% (54) postmenopausal bleeding 13% (14) postmenopausal, unscheduled bleeding with HRT or tamoxifen

[a] Missing parity data in 14 cases.

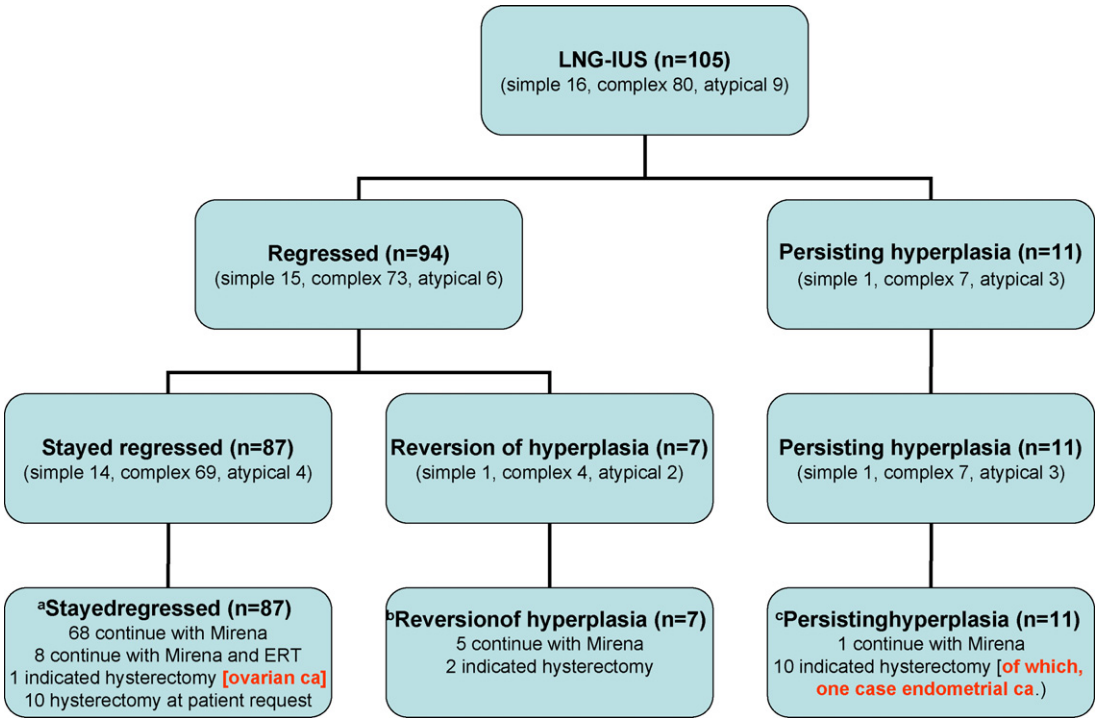

Fig. 1. Outcome of study according to outpatient endometrial Pipelle histology at pre-treatment and 2-years following LNG-IUS insertion. [a]Of the 10 hysterectomies at patient request from the stayed regressed group, histologies from the uteri showed nine regressed uteri and one atypical endometrial hyperplasia. This is further explained in Table 2, footnote c. [b]Of the seven reverted hyperplasias, all were non-atypical hyperplasias on Pipelle, all were offered hysterectomy, five declined hysterectomy in favour of continuing with LNG-IUS. Of the two indicated hysterectomies performed, histological analysis showed one had regressed and one had complex hyperplasia. [c]Of the 11 persisting hyperplasias, all were offered hysterectomy, one declined hysterectomy in favour of continuing with LNG-IUS. Of the 10 indicated hysterectomies performed, histological analysis showed two had regressed, one simple, four complex, two atypical hyperplasias persisted and one case of Stage 1A endometrial cancer.

Survival analysis methods (Kaplan–Meier, Cox proportional hazard) showed there was no statistically significant difference between the types of hyperplasia in terms of the time interval to regression (Table 2). The overall mean interval to regression was 9 months (95% CI 7.0–11.1) for the overall group (Table 2). Furthermore, survival analysis showed no statistically significant association of baseline covariates (age, parity, menopausal status, BMI, diabetes, hypertension, exogenous estrogen or tamoxifen use) on the rate of regression.

3.3. Endometrial hyperplasia associated with hormone replacement therapy (HRT)

Of the 22 cases of HRT associated endometrial hyperplasia and treated subsequently with LNG-IUS, 2 stopped HRT, 17 continued with cyclic combined HRT and 3 opted for estrogen only HRT. All were non-atypical hyperplasias (19 complex and 3 simple), and all, apart from one case, showed endometrial regression with LNG-IUS therapy. The non-regressed complex hyperplasia

Table 2
Outcome of the study according to histological data derived from outpatient endometrial Pipelle and hysterectomy histologies

Endometrial hyperplasia (number of cases at study commencement)	Total number of cases regressing with LNG-IUS	[a]Mean time for regression (months) and 95% confidence limits	Proportion achieving regression[b] by 12 months of LNG-IUS	Proportion achieving regression[b] by 24 months of LNG-IUS
Simple ($n = 16$)	15 (94%)	6.2 (4.4–8.0)	15/16	15/16
Complex ($n = 80$)	73 (92%)	9.4 (7.0–11.7)	69/80	73/80
Atypical ($n = 9$)	6 (67%)	8.2 (5.2–11.3)	6/9	6/9
Overall group ($n = 105$)	94 (90%)	9.0 (7.0–11.1)	[c]90/105	[c]94/105

[a] There are no statistically significant differences in probabilities of regression over time between simple, complex and atypical hyperplasias [Kaplan–Meier Log Rank Mantel-Cox ($p = 0.20$)].

[b] Data on histological regression is derived from combined use of outpatient endometrial Pipelle and hysterectomy histologies.

[c] Two of the 94 cases that showed regression on Pipelle, were subsequently identified to have atypical hyperplasia (one case, formerly simple hyperplasia) and ovarian cancer (one case, formerly complex hyperplasia). The former case underwent hysterectomy at patient request due to troublesome abnormal bleeding side effects with LNG-IUS despite Pipelle regression. The latter case underwent hysterectomy as this was indicated through ongoing sonographic surveillance for a postmenopausal cyst concurrent with the regressed Pipelle. Both cases were identified within 1 year of LNG-IUS treatment.

underwent hysterectomy and uterine histology subsequently confirmed endometrial regression had in fact occurred. There was a single case of tamoxifen associated complex hyperplasia which initially regressed with LNG-IUS then reverted back to complex hyperplasia; uterine histology at hysterectomy confirmed complex hyperplasia.

3.4. Two cases of cancer

Two cases of cancer were identified. One case was Stage 1B ovarian cancer, which had been identified in a complex hyperplasia that had regressed at 3 months with LNG-IUS but had been under ultrasonographic surveillance for a persistent postmenopausal ovarian cyst. The other case was Stage 1A endometrial cancer, which had been identified in a case of complex hyperplasia that had shown non-regression at 12 months with LNG-IUS and therefore underwent indicated hysterectomy (Fig. 1).

3.5. Hysterectomy and correlation with endometrial Pipelle

Hysterectomy occurred in 23/105 women, and a summary of the origin and indication for hysterectomy is shown in Fig. 1. Most hysterectomies (12/23) were performed for persisting hyperplasia and reversion to hyperplasia following initial regression to normal histology. However, 10/23 hysterectomies were performed in women with endometrial regression on Pipelle histology. The reasons cited included: worsening or persistence of abnormal bleeding symptoms (3), patient request (4), patient fear of progression to cancer (1), uterine prolapse (1) and concurrent cervical intraepithelial neoplasia (1). In all these cases the endometrium was extensively sampled, including the cornual aspects, and showed changes secondary to the local progestogen therapy without any evidence of hyperplasia. Using histology of the uterus at hysterectomy as the ''gold standard'' and the preceding endometrial Pipelle biopsy as a diagnostic test, then Pipelle had a sensitivity of 83% and specificity of 73% for identifying endometrial regression (Table 3).

4. Discussion

LNG-IUS is highly effective at treating endometrial hyperplasia, irrespective of whether non-atypical or atypical hyperplasia is being treated. Beneficial effects are observed by the majority within 1 year of treatment. Treatment success can be reliably monitored through regular 6-monthly outpatient endometrial Pipelle surveillance. Future widespread use of LNG-IUS to treat non-atypical hyperplasias is likely to reduce the number of hysterectomies performed for this condition, and thereby avoid exposing women to unwarranted surgical risks.

This is the largest published series of the use of LNG-IUS to treat endometrial hyperplasia [9–15]. Furthermore, we believe this is the first study to examine the use of LNG-IUS to treat endometrial hyperplasia occurring in HRT users. The prospective design and strict data collection proforma used in this study ensured uniform inclusion/exclusion criteria and reliable collection of all outcome measures. The study was designed as a pragmatic measure of the effectiveness of LNG-IUS at 1 and 2-years, therefore our results are applicable to current clinical practice.

Our study could be criticised for not incorporating a control (expectant management) or cohort (e.g. oral progestogens) comparison group. Furthermore, our study is under-powered to detect genuine differences in subtypes of endometrial hyperplasia, as well as investigate their significance along with other covariates (e.g. diabetes, hypertension, HRT) on the likelihood of regression with LNG-IUS treatment.

It has been established that outpatient endometrial biopsy is accurate in diagnosing endometrial hyperplasia [21]. However, we accept there may be uncertainty in our estimations of sensitivity and specificity of endometrial Pipelle in correlating to uterine histology. This is because we only performed hysterectomy and obtained 'gold standard' uterine histology in around a quarter of study participants, and there may be differences in histological criteria used by others and our own group. Nonetheless, by finding similar degrees of test accuracy as previous authors [6,22–25] we believe our results are at least consistent with the published literature. Furthermore, we minimised the histopathological bias by utilising strict predefined histological criteria and limiting the histological interpretation to two experienced histopathologists.

Overall, our study's 90% (94/105) endometrial regression rate incorporates regression rates of 92% (88/96) and 67% (6/9) for non-atypical and atypical hyperplasias, respectively. A higher regression rate of 95% (19/20) with regression rates of 100% (12/12) and 88%(7/8) for non-atypical and atypical hyperplasias had been observed in a

Table 3
Correlation between endometrial Pipelle histology and hysterectomy histology ($n = 23$ hysterectomies)

	Uterine histology at hysterectomy	
	Regressed endometrium	Not regressed endometrium
Endometrial Pipelle biopsy		
Test positive: showing regression	10	3
Test negative: showing non-regression	2	8

Sensitivity 83%, specificity 73%, likelihood ratio (95% confidence interval), LR (positive test) 3.06 (1.23–8.74), LR (negative test) 0.23 (0.06–0.70).

recently published long-term study [9]. This difference could be explained by the longer duration of follow up in the published study [9]. Nevertheless, our study's non-atypical regression rate is similar to the oral progestogen treatment regression rate (93%, $n = 134$) [26] and exceeds the expectantly managed regression rate of 72% (93/129) identified by pooling studies [4–6]. This study's atypical regression rate does not significantly differ from the expectant regression rate of 54% (15/28) identified from the same pooled studies. Importantly, this study suggests a trend for intrauterine progestogen therapy to regress non-atypical rather than atypical hyperplasia, which is a finding that has also been suggested by other groups [9,26–30].

We would have expected LNG-IUS use in our study to have led to a greater reduction in hysterectomy treatment for hyperplasia. However, for a variety of unexpected reasons (e.g. personal choice, fear of progression) in addition to those due to failed medical treatment or unwanted side-effects with LNG-IUS, women opted for hysterectomy. We were unable to further explore how such patient preferences could impact on patient satisfaction, compliance and cost-effectiveness of LNG-IUS compared to hysterectomy treatment alternatives. Furthermore, as we were dealing with a pre-malignant condition, in an age group not requiring to conserve the uterus for fertility, this would lead to an increased risk of favouring a hysterectomy decision, irrespective of whether endometrial regression had been successful or unsuccessful.

Both cases of cancer identified in the study were Stage I tumours, and were readily identified within 1 year of insertion of LNG-IUS. It could be argued that earlier hysterectomy, instead of LNG-IUS medical treatment, would have prevented cancer development or improved prognosis if cancer was identified earlier. In this context, our study suggests around 50 hysterectomies would be needed to prevent (NNT) one case of gynaecological cancer in women with endometrial hyperplasia.

Oral progestagens and hysterectomy are widely accepted treatment options for endometrial hyperplasia [6–8]. Newer therapies under evaluation include endometrial ablation [31] and aromatase inhibitors [32]. Nonetheless, we believe that the success of this study, utilising LNG-IUS therapy, should provide an impetus for future robust randomised controlled trials to evaluate the effectiveness of medical and surgical treatments in treating endometrial hyperplasia. Successful validation of the treatment potential of LNG-IUS for endometrial hyperplasia will undoubtedly reduce the number of women undergoing hysterectomies for this condition and avoid exposing them to unwarranted surgical risks.

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